Practitioner's Docket No. 56513 (45107)

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US) (ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/EP00/04360	16 May 2000	18 May 1999
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

A TRANSDERMAL THERAPEUTIC SYSTEM (TTS) CONTAINING TOLTERODINE
TITLE OF INVENTION

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APPLICANTS

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended 37 C F.R. § 1.495.

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C F R. §1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F R. §1.8.*

NOTE. Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111 37 C F R § 1 494(f).

CERTIFICATION UNDER 37 C.F.R. § 1.10*
*(Express Mail label number is **mandatory.**)*
(Express Mail certification is optional.)

I hereby certify that this paper, along with any document referred to, is being deposited with the United States Postal Service on this date November 16, 2001, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number **EL895419993US**, addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Susan M Dillon
(type or print name of person mailing paper)

Susan M. Dillon
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1 10(b).*
*"Since the filing of correspondence under § 1 10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [X] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [X] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2. Fees

CLAIMS FEE [ ]*	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS	9 - 20 =	0	x $ 18.00 =	$0
	INDEPENDENT CLAIMS	2 - 3 =	0	x $ 80.00 =	$0
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $270.00				$0
BASIC FEE**	[ ] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) ..... $100.00 [ ] and the above requirements are not met (37 CFR 1.492(a)(1)) ..... $710.00 [X] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the USPTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 CFR 1.492(a)(2)) ..... $740.00 [ ] has not been paid (37 CFR 1.492(a)(3)) ..... $1040.00 [X] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $890.00				$890.00
	Total of above Calculations				= $890.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed. (note 37 CFR 1.9, 1.27, 1.28)				- $
	Subtotal				$890.00
	Total National Fee				$890.00
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				$0
TOTAL	Total Fees enclosed				$890.00

   i. [X] A check in the amount of $890.00 to cover the above fees is enclosed.

   ii. [ ] Please charge Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

**WARNING *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office 37 C F.R § 1 495(b)(2). The payment of the surcharge set forth in § 1 492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. [X] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE. *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20 At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below*

a. [ ] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [X] has been transmitted
   i. [X] by the International Bureau.
   Date of mailing of the application (from form PCT/IB/308):
   ii. [ ] by applicant on _____.
   Date

4. [X] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
a. [X] is transmitted herewith.
b. [ ] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on _____.
   Date
d. [ ] will follow.

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE: *The Notice of January 7, 1993 points out that 37 C F.R § 1 495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that. "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1 121 In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.*

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): _____.

ii. [ ] by applicant on _____.
Date

c. [X] have not been transmitted as
i. [X] applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210): **12/5/00**
ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
a. [ ] is transmitted herewith.
b. [ ] is not required as the amendments were made in the English language.
c. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [X] A copy of the international examination report (PCT/IPEA/409)
[X] is transmitted herewith.
[ ] is not required as the application was filed with the United States Receiving Office.

8. [X] Annex(es) to the international preliminary examination report
a. [X] is/are transmitted herewith.
b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [X] A translation of the annexes to the international preliminary examination report
a. [X] is transmitted herewith.
b. [ ] is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115
a. [ ] was previously submitted by applicant on _____.
Date
b. [X] is submitted herewith, and such oath or declaration
i. [ ] is attached to the application.
ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.
iii. [X] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
a. [X] is transmitted herewith.
b. [ ] has been transmitted by the International Bureau.
Date of mailing (from form PCT/IB/308): _____.
c. [ ] is not required, as the application was searched by the United States International Searching Authority.
d. [ ] will be transmitted promptly upon request.

e. [ ] has been submitted by applicant on _____.
Date

12. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
a. [X] is transmitted herewith.
Also transmitted herewith is/are:
[X] Form PTO-1449 (PTO/SB/08A and 08B).
[X] Copies of citations listed.
b. [ ] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
c. [ ] was previously submitted by applicant on _____.
Date

13. [ ] An assignment document is transmitted herewith for recording.

A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [X] FORM PTO 1595 is also attached.

_____
_____
_____

14. [X] Additional documents:
a. [X] Copy of request (PCT/RO/101)
b. [X] International Publication No. WO 00/69421
i. [ ] Specification, claims and drawing
ii. [X] Front page only
c. [ ] Preliminary amendment (37 C.F.R. § 1.121)
d. [X] Other

PCT/RO/101

15. [X] The above checked items are being transmitted
a. [X] before 30 months from any claimed priority date.
b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

_____
_____
_____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all

required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: *"Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).*

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. **04-1105.**

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[X] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: *Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.*

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[ ] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: *Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b)*

NOTE: *37 C.F R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

Reg. No.: 33,860

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#129647

A transdermal therapeutic system (TTS) containing tolterodine

Description

The present invention relates to a transdermal therapeutic system (TTS) for the transcutaneous administration of tolterodine over several days, and to methods of producing said TTS.

The bioavailability of active ingredients which are administered orally is often unsatisfactory. The intravenous administration of active ingredients is frequently unpleasant and unsatisfactory for patients. In the bile duct, the hepatic metabolisation of many active ingredients can result in undesirable concentration ratios, toxic by-products and in a reduction of efficacy, or even in a loss of efficacy. Compared with oral administration, transdermal administration of active ingredients has various advantages. The supply of active ingredient can be better controlled over a longer period, whereby high blood level fluctuations are avoided. Moreover, the requisite therapeutically effective dose can usually be considerably reduced. Furthermore, patients often prefer a patch to pills which have to be taken once or many times a day.

In the past, there has been a multiplicity of transdermal therapeutic systems (TTS) of different structures which have been proposed for different active ingredients in order to overcome the aforementioned disadvantages of the non-transdermal administration of active ingredients.

Thus the technical documents listed below describe systems for the parenteral administration of a broad multiplicity of active ingredients which react systemically or locally; these systems are based either on a controlled dose or on the overall release of active ingredient.

Examples thereof include US (United States Patents)
3,598,122A; 3,598,123A, 3,731,683A, 3,797,494A; 4,031,894A; 4,201,211 A;
4,286,592 A; 4,314,557 A; 4,379,454 A: 4,435,180 A; 4,559,222 A; 4,568,343 A;

4,573,995 A, 4,588,580 A; 4,645,502 A; 4,702,282 A; 4,788,062 A; 4,816,258 A; 4,849,226 A; 4,908,027 A: 4,943,435 A and 5,004,610 A.

In the late sixties of this century, however, it was initially assumed, based on theoretical considerations, that any active ingredient exhibiting a short half-life, high efficacy and good permeation through the skin was suitable for reliable and effective administration by means of a TTS. However, it was not possible to realise these initial expectations regarding the possibility of the transdermal administration of active ingredients by means of a TTS. The reason for this is mainly that skin has been provided by nature with a variety of insuperable qualities in order to maintain its function as an intact barrier to the ingress of extraneous substances into the body (in this respect, see: Transdermal Drug Delivery: Problems and Possibilities, B.M. Knepp et al., CRC Critical Review and Therapeutic Drug Carrier Systems, Vol. 4, Issue 1 (1987)).

Therefore, transdermal administration is available only for those few active ingredients which comprise a suitable combination of many favourable characteristics. The requisite characteristics, which ensure reliable and effective transdermal administration, cannot be predicted for a given substance, however.

The requirements imposed on an active ingredient which is suitable for transdermal administration are:

- capable of passing through the skin,
- no impairment of the adhesive capacity of the patch by the active ingredient,
- avoidance of skin irritation,
- avoidance of allergic reactions,
- favourable pharmacokinetic properties,
- favourable pharmacodynamic properties,
- a relatively wide therapeutic window,
- metabolic properties which are consistent with therapeutic use comprising continuous delivery.

The above list of requirements is undoubtedly not exhaustive. So that an active ingredient can be available for transdermal administration, the "correct" combination all of these requirements is desirable.

The aforementioned requirements for the active ingredient apply similarly to the TTS composition which contains the respective active ingredient and the nature of the structure thereof.

Transdermal therapeutic systems (TTS) are usually patches which are provided with an impermeable outer layer, a peelable protective layer and a matrix which contains an active ingredient, or a reservoir which contains an active ingredient and comprises a semipermeable membrane. In the first case these are termed matrix patches, and in the second case they are termed membrane systems.

The substances used for the outer layer are usually polyesters, polypropylene, polyethylene, polyurethane etc., which can also be metallised or pigmented. Suitable substances for the peelable protective layer include polyesters, polypropylene and also paper with a silicone and/or polyethylene coating. Fluoropolymers are also used.

A multiplicity of substances, such as those based on polyacrylate, silicones, polyisobutylene, butyl rubber, styrene/butadiene copolymers or styrene/isoprene copolymers, can be used as the matrix which contains the active ingredient.

The membranes which are used in membrane systems can be microporous or semipermeable, and are usually based on an inert polymer, particularly polypropylene, polyvinyl acetate or silicones.

Whereas matrix compositions which contain an active ingredient can be self-adhesive, matrix compositions which contain an active ingredient but which are not self-adhesive can also be used depending on the active ingredient used, but the structure of the patch or TTS consequently has to be provided with an overtape.

To ensure the requisite flux of active ingredient, skin penetration enhancers are frequently necessary as additives, such as aliphatic, cycloaliphatic and/or aromatic-aliphatic alcohols, each of which is monohydric or polyhydric and contains up to 8 C atoms, alcohol/water mixtures, saturated and/or unsaturated fatty alcohols which each contain 8 to 18 carbon atoms, saturated and/or unsaturated fatty acids which each contain 8 to 18 carbon atoms and/or esters thereof, as well as vitamins.

Moreover, stabilisers such as polyvinyl pyrrolidone, α-tocopherol succinate, propyl gallate, methionine, cysteine and/or cysteine hydrochloride are frequently added to the matrix which contains the active ingredient.

As shown by the above statements, numerous TTS structures and materials which are used therefor are known. However many interacting requirements have to be taken into account if a drug in form of a TTS is to satisfy a medical need.

The following problems have to be taken into account during the development of a TTS containing an active ingredient:

1. The permeability of the skin to the active ingredient may be too low to achieve the therapeutically necessary rate of penetration, and/or the delay time ("lag-time") until the therapeutically necessary plasma level is reached is too long, with the consequence that additives which increase the rate of penetration through the skin have to be administered.

2. The polymer matrix which contains the active ingredient, and which optionally contains skin penetration enhancers in addition, may not be physically stable over an extended period of storage. In particular, recrystallisation of the active ingredient may occur, which results in an uncontrollable decrease in the capacity of the TTS to release active ingredient.

3. For self-adhesive polymer films, a high content of active ingredient and/or of skin penetration enhancers in the polymeric backing material makes it difficult to achieve the optimum adhesive properties for the transdermal system.

4. For applications comprising several days of administration, the rate of resorption of the active ingredient decreases in an unacceptable manner, so that additional control layers and/or control components are necessary.

5. Furthermore, it is known from the literature that the fatty acid esters of polyhydric alcohols which are frequently used to promote penetration through the skin contain impure blending agents of variable quality. This results in increases in penetration which exhibit poor reproducibility (Burkoth et al. 1996, DE 196 22 902 A1).

The problems described above have therefore given rise to a multiplicity of designs of transdermal therapeutic systems, which are reflected in the prior art in this field.

DE 196 53 606 A1 describes an adhesive and bonding agent for a TTS comprising defined quantitative proportions of the components a), a (meth)acrylate polymer which may contain quaternary ammonium groups, b) an organic di- or tricarboxylic acid, and c), a plasticiser, which can be a triester of citric acid.

As shown by the above statements, many patch structures are known, as are the materials used therefor. Nevertheless, for many active ingredients which are processed to form transdermal therapeutic systems there has hitherto been a considerable need for TTS systems which facilitate the release of active ingredient as required by the therapy concerned without involving costly structures, and which comprise the optimum relationships with regard to their constituents overall. This also applies to the active ingredient tolterodine if this is to be administered transcutaneously.

Tolterodine is the international non-proprietary name (INN) for the R-isomer of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (IUPAC description:

(+)-(R)-2-{α[2-(diisopropylamino)ethyl]benzyl}4-methylphenol)). The term "tolterodine" is employed hereinafter to mean N,N-diisopropyl-3-(2-hydroxy-5-ethylphenyl)-3-phenylpropylamine. Inasmuch as reference is made to the individual isomers, namely the R- or S-isomer or a racemic mixture of the R- and S-isomers, these are referred to as R-, S- and R,S-tolterodine, respectively.

Tolterodine is used therapeutically for the treatment of bladder instability associated with the symptoms of involuntary discharge of urine, pollakiuria and urinary incontinence. The recommended dose is 2 mg of tolterodine twice daily, and is administered orally.

After oral application, tolterodine is metabolised to very different degrees in the bile duct. Thus the absolute bioavailability of tolterodine is 65 % for slow metabolisers, but is only 17 % for rapid metabolisers. Since even the resulting 5-hydroxymethyl metabolite is pharmacologically active, , the reduced tolterodine blood level does not result in any loss of efficacy with rapid metabolisers. Nevertheless, it is desirable that fluctuations such as these between individuals are avoided and that differences in efficacy which result therefrom are avoided. Moreover, different plasma levels occur if tolterodine is administered with or without the ingestion of food. In principle, these problems can be avoided by the transdermal administration of tolterodine, since the active ingredient is then supplied directly to the blood circulation without passing through the gastro-intestinal tract and the bile duct. The plasma fluctuations comprising high concentration peaks which occur with oral administration, and which result in undesirable side-effects such as dry mouth, dyspepsia, sickness, accommodation problems and confusion, can be avoided by transdermal administration. Similarly, levels of active ingredient which decrease below the threshold of efficacy, and the involuntary, round the clock discharge of urine can be avoided. Furthermore, the liver is subjected to considerably less loading by the active ingredient due to the avoidance of the bile duct, which is especially desirable for patients with a pre-damaged liver, such as patients with cirrhosis of the liver, for example.

WO 98/03067 A1 teaches the use of S-tolterodine for the treatment of bladder voiding disorders, including incontinence. Amongst other methods, transdermal application is also proposed there for the administration of the active ingredient. However, the aforementioned patent contains no technical teaching on the implementation of transdermal application and does not contain an example which relates thereto.

Transdermal therapeutic systems for the administration of tolterodine are not described in the prior art.

The object of the present invention is therefore to provide a TTS for tolterodine. The TTS should be of simple structure, should exhibit good compatibility with the skin, should be physically and chemically stable over extended periods of storage, should possess good properties of adhesion, and should release as much active ingredient per unit area as possible, both on and through the skin.

This object has been achieved by providing a transdermal therapeutic system (TTS) for the transcutaneous administration of tolterodine which contains a self-adhesive matrix material in the form of a layer, which layer contains a (meth)acrylate copolymer comprising ammonium groups, at least one plasticiser, and up to 25 % by weight tolterodine. Surprisingly, tolterodine is released on and through the skin therefrom at a high rate of release which for other active ingredients is only known in combination with skin penetration enhancers. Consequently, the dose which is therapeutically necessary can be administered using a TTS with a small release surface, without having to accept an increased risk of skin irritation due to skin penetration enhancers.

In the sense of the present invention, the terms "several days" and "solid solution" are to be understood as follows:

a) "several days": for therapeutic use, the TTS can be applied to the skin for a period of from 1 to 7 days, preferably from 1 to 4 days.

b) "solid solution": the pharmaceutical active ingredient is distributed in the form of dispersed molecules in the TTS matrix.

According to another embodiment of the invention, the TTS systems described above can be additionally surrounded on the skin, with the exception of the release surface of the matrix which contains tolterodine, by a larger dermal plaster which is free from active ingredient, for fixing to the skin at the point of application (overtape).

This structure results in the advantage that different skin types and climatic zones can be taken into account. Moreover, firstly the co-adhesion/adhesion properties, and secondly the solubility, rate of dissolution and release properties of the active ingredient, can be optimised substantially independently of each other.

The matrix which contains the active ingredient preferably contains (R,S)-tolterodine or R-tolterodine.

According to another embodiment of the invention, the matrix material contains deuterated tolterodine as an active ingredient. Deuterated tolterodine is obtained by replacing one or more hydrogen atoms by deuterium, which is an isotope thereof. In principle, any hydrogen atom which the tolterodine contains can be replaced by deuterium. The methyl substituent of the aromatic moiety, or the aromatic moiety itself, preferably contains at least one deuterium atom.

An example thereof is 2-(3-diisopropylamino-1-phenylpropyl)-4-[$^2H_3$]methyl-phenol.

It has surprisingly been found that the rate of dermal penetration of deuterated tolterodine is considerably increased compared with that of non-deuterated tolterodine, which exhibits a very high rate of dermal penetration anyway.

According to a further embodiment, the matrix material preferably contains 10 - 20 % by weight of tolterodine.

Finally, the matrix material which contains an active ingredient can be a solid solution.

The formation of a solid solution of tolterodine in the (meth)acrylate polymer which contains ammonium groups could not have been anticipated, and is all the more surprising because many active ingredients do not form solid solutions (comprising a distribution of dispersed molecules) in polymers, but are incorporated in the form of solid particles in the polymer concerned, as can be identified by electron microscopy. In contrast to solid solutions, crystalline materials also exhibit a Debye-Scherrer pattern.

According to another embodiment of the invention, the matrix material which contains tolterodine contains at least one triester of citric acid. The triester of citric acid preferably contains short chain alkanoic acids, particularly suitable examples of which include methanoic acid, ethanoic acid, n-propanoic acid, i-propanoic acid, n-butanoic acid, sec.- butanoic acid and tert.-butanoic acid.

In one preferred embodiment, the matrix material which contains tolterodine contains n-butyl citrate, ethyl citrate or a mixture thereof.

Based on the composition according to the invention and to the structural form of the TTS, it is surprising that satisfactory physical stability of the system is ensured on long-term storage, despite high concentrations of active ingredient in the polymer matrix.

It could not have been anticipated that the polymer which is used as the polymer matrix which contains the active ingredient, after being adhesively bonded to the skin, would result in intimate contact between the matrix material and the skin, of a quality such that a TTS is formed which is self-adhesive for several days and which satisfies both therapeutic and economic requirements, particularly those requirements related to commercial economics.

At the same time, patient compliance is taken into account to a very considerable extent.

If the embodiment comprising a dermal patch which is free from active ingredient and an overtape is selected, it is only necessary to employ dermal patches of small area which comprise an adhesive edge only a few mm wide.

This is both economic and is an advantage with regard to patient compliance.

According to another embodiment of the invention, the backing film of the TTS comprises a metallised coating or oxide coating on its matrix side.

The structure of the TTS according to the invention is illustrated in drawings 1 and 2.

Drawing 1 shows the embodiment without an overtape, consisting of a polymer matrix (1) which contains an active ingredient, a removable protective film (5) and a covering film (2).

Drawing 2 shows the embodiment which does comprise an overtape. In addition to the layers which are contained in the embodiment illustrated in drawing 1, it contains an overtape comprising a backing film (4) and an adhesive film (3).

The TTS according to the invention can be produced by what is termed the "solvent-based process". For this purpose, the polymer, active ingredient and the other constituents are dissolved in a common solvent and the solution obtained is distributed as a thin layer on a support. The coated support is dried in order to remove the solvent contained in the polymer matrix, is covered by a further film and is finally separated into pieces of the desired size.

Alternatively, the TTS can also be produced by what is termed the "hot melt process". For this purpose, the polymer is melted and mixed with the active ingredient and with the other auxiliary materials, and the mixture obtained is distributed as a thin layer on a support (=removable protective film) and is allowed to cool. It is covered with another film (covering film) and is separated into pieces of the desired size.

The matrix which contains tolterodine is preferably produced by melt extrusion, wherein the active constituent is continuously metered, as a solid substance, into a melt comprising a polymer and a plasticiser, and the polymer melt which is obtained, and which contains the active ingredient, is continuously coated, immediately the active ingredient has been added, on to a removable protective layer as a coat of thickness ranging from 0.02 to 0.5 mm, and the double layer laminate which is obtained is provided with an outer layer on the other side of the matrix. The matrix material which contains the active ingredient is preferably produced and further processed in one continuous, cost-saving operation comprising short processing times. Thermal loading of the polymer material which contains the active ingredient is reduced to a minimum, so that decomposition reactions are prevented.

The invention is explained with reference to the following examples:

Example 1

2.52 g Eudragit RS 100, (= poly(ethyl acrylate, methyl methacrylate, trimethylammonio-ethyl methacrylate chloride), with a molar ratio of monomer units of 1:2:0.1),
1.16 g tributyl citrate, and
0.65 g R-tolterodine, were dissolved in a glass beaker with stirring, with the addition of 8.00 g ethyl acetate.

The polymer solution which was obtained was spread, using a doctor blade, on to a peelable polyester film (= backing film) of thickness about 100 μm which had been metallised with aluminium and provided with a silicone coating on both sides, and was dried for 30 minutes at 45°C in a recirculating air oven, so that a polymer film which contained tolterodine was obtained which had a weight per unit area of 110 g/m^2. The latter was subsequently covered with a polyester film of thickness about 19 μm. Transdermal systems (TTS) of size 5 cm^2 were punched out from the 3-layer laminate

which was thus obtained, and consisted of a peelable protective layer, a polymer film containing the active ingredient and a covering film.

Tolterodine flux measurements in vitro

Flux measurements through mouse skin

A TTS with a punched-out area of 2.55 cm^2 was fixed to the epidermal side of skin from the stomach and back of hairless mice in a horizontal diffusion cell. Immediately thereafter, the acceptor chamber of the cell was filled, free from air bubbles, with a phosphate buffer solution (0.066 molar) at pH 6.2, which had been preheated to 32°C, and the release medium was maintained at a controlled temperature of 32 ± 0.5°C using a thermostat.

When samples were taken (after 3, 6, 24, 30, 48, 54 and 72 hours), the medium was replaced by fresh medium at a controlled temperature of 32 ± 0.5°C.

Flux measurements through human skin

Testing was performed in a flow cell as described by Tiemessen (Harry L.G.M. Thiemessen et al., Acta Pharm. Technol. 34 (1988), 99-101), on freshly prepared, human skin approximately 200 µm thick, which rested on a silicone membrane facing the acceptor cell (acceptor medium: phosphate buffer solution, 0.066 molar, pH 6.2; at a controlled temperature of 32 ± 0.5°C.

Samples were taken after 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72 hours.

In these tests on human skin, the content of R-tolterodine base in the release- and acceptor medium was determined by high-performance liquid chromatography under the following conditions: stationary phase: C_8 inversion phase, 3.9 x 150 mm, 5 µm; column temperature = room temperature; eluent: 700 parts by volume of sodium dihydrogen phosphate buffer (0.05 mol), pH 3.0, 300 parts by volume of acetonitrile; Detection: UV at 220 nm; flow rate: 1.2 ml/min, injection volume: 50 µl at 15°C.

The test results for Example 1 are presented in Table 1.

Table 1:

Flow rates of R-tolterodine base through an excised skin preparation (Example 1) Ch.-B. INZ 006)

	Content of R-tolterodine base [% by weight]	Mean cumulative flux [µg/cm^2] after		
		24 hours	48 hours	72 hours
Mouse skin (n = 4)	15.0	524.2	849.0	1036.4
Human skin (n = 3)	15.0	130.5	460.1	731.0

Example 2

9.71 g Eudragit RS 100, (= poly(ethyl acrylate, methyl methacrylate, trimethylammonio-ethyl methacrylate chloride), with a molar ratio of monomer units of 1:2:0.1),

4.76 g tributyl citrate, and

2.50 g (R,S)-tolterodine were dissolved in a glass beaker with stirring, with the addition of

32.00 g ethyl acetate.

The polymer solution which was obtained was spread, using a doctor blade, on to a peelable polyester film (= backing film) of thickness about 100 µm which had been metallised with aluminium and provided with a silicone coating on both sides, and was dried for 30 minutes at 45°C in a recirculating air oven, so that a polymer film which contained tolterodine was obtained which had a weight per unit area of 125 g/m^2. The latter was subsequently covered with a polyester film of thickness about 19 µm

(=covering film). Transdermal systems (TTS) of size 5 cm^2 were punched out from the 3-layer laminate which was thus obtained, and consisted of a peelable protective layer, a polymer film containing the active ingredient, and a covering film.

Tolterodine flux measurements in vitro

Flux measurements through mouse skin

A TTS with a punched-out area of 2.55 cm^2 was fixed to the epidermal side of skin from the stomach and back hairless mice in a horizontal diffusion cell. . Immediately thereafter, the acceptor chamber of the cell was filled, free from air bubbles, with a phosphate buffer solution (0.066 molar) at pH 6.2, which had been preheated to 32°C, and the release medium was maintained at a controlled temperature of 32 ± 0.5°C using a thermostat.

When samples were taken (after 3, 6, 24, 30, 48, 54 and 72 hours), the medium was replaced by fresh medium at a controlled temperature of 32 ± 0.5°C.

Flux measurements through human skin

Testing was performed in a flow cell as described by Tiemessen (Harry L.G.M. Thiemessen et al., Acta Pharm. Technol. 34 (1988), 99-101), on freshly prepared, human skin approximately 200 µm thick, which rested on a silicone membrane facing the acceptor cell (acceptor medium: phosphate buffer solution, 0.066 molar, pH 6.2; at a controlled temperature of 32 ± 0.5°C.

Samples were taken after 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72 hours.

In these tests on human skin, the content of (R,S)-tolterodine base in the release- and acceptor medium was determined by high-performance liquid chromatography under the following conditions: stationary phase: C_8 inversion phase, 3.9 x 150 mm, 5 µm; column temperature = room temperature; eluent: 700 parts by volume of sodium

dihydrogen phosphate buffer (0.05 mol), pH 3.0, 300 parts by volume of acetonitrile; Detection: UV at 220 nm; flow rate: 1.2 ml/min, injection volume: 50 µl at 15°C.

The test results for Example 2 are presented in Table 2.

Table 2:

Flow rates of (R,S)-tolterodine base through an excised skin preparation (Example 2) Ch.-B. INZ 007)

	Content of (R,S)-tolterodine base [% by weight]	Mean cumulative flux [µg/cm^2] after		
		24 hours	48 hours	72 hours
Mouse skin (n = 4)	15.0	648.8	1110.4	1302.0
Human skin (n = 3)	15.0	208.4	718.9	1219.4

Example 3

9.71 g Eudragit RS 100, (= poly(ethyl acrylate, methyl methacrylate, trimethylammonio-ethyl methacrylate chloride), with a molar ratio of monomer units of 1:2:0.1),

4.76 g tributyl citrate, and

2.50 g R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-[$^2H_3$]methylphenol(R-D_3)-tolterodine) were dissolved in a glass beaker with stirring, with the addition of 32.00 g ethyl acetate.

The polymer solution which was obtained was spread, using a doctor blade, on to a peelable polyester film (= backing film) of thickness about 100 µm which had been metallised with aluminium and provided with a silicone coating on both sides, and was dried for 30 minutes at 45°C in a recirculating air oven, so that a polymer film which contained tolterodine was obtained which had a weight per unit area of 125 g/m^2. The

latter was subsequently covered with a polyester film of thickness about 19 μm. Transdermal systems (TTS) of size 5 cm^2 were punched out from the 3-layer laminate which was thus obtained, and consisted of a peelable protective layer, a polymer film containing the active ingredient and a covering film.

Tolterodine flux measurements in vitro

Flux measurements through mouse skin

A TTS with a punched-out area of 2.55 cm^2 was fixed to the epidermal side of skin from the stomach and back hairless mice in a horizontal diffusion cell. Immediately thereafter, the acceptor chamber of the cell was filled, free from air bubbles, with a phosphate buffer solution (0.066 molar) at pH 6.2, which had been preheated to 32°C, and the release medium was maintained at a controlled temperature of 32 ± 0.5°C using a thermostat.

When samples were taken (after 3, 6, 24, 30, 48, 54 and 72 hours), the medium was replaced by fresh medium at a controlled temperature of 32 ± 0.5°C.

In these tests on mouse skin, the content of R-(D_3)-tolterodine base in the release- and acceptor medium was determined by high-performance liquid chromatography under the following conditions: stationary phase: C_8 inversion phase, 3.9 x 150 mm, 5 µm; column temperature = room temperature; eluent: 700 parts by volume of sodium dihydrogen phosphate buffer (0.05 mol), pH 3.0, 300 parts by volume of acetonitrile; Detection: UV at 220 nm; flow rate: 1.2 ml/min, injection volume: 50 µl at 15°C.

Flux measurements through human skin

Testing was performed in a flow cell as described by Tiemessen (Harry L.G.M. Thiemessen et al., Acta Pharm. Technol. 34 (1988), 99-101), on freshly prepared, human skin approximately 200 µm thick, which rested on a silicone membrane facing the acceptor cell (acceptor medium: phosphate buffer solution, 0.066 molar, pH 6.2; at a controlled temperature of 32 ± 0.5°C.

Samples were taken after 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72 hours.

In these tests on human skin, the content of R-(D_3)-tolterodine base in the release- and acceptor medium was determined by high-performance liquid chromatography under the following conditions: stationary phase: C_8 inversion phase, 3.9 x 150 mm, 5 µm; column temperature = room temperature; eluent: 700 parts by volume of sodium dihydrogen phosphate buffer (0.05 mol), pH 3.0, 300 parts by volume of acetonitrile; Detection: UV at 220 nm; flow rate: 1.2 ml/min, injection volume: 50 µl at 15°C.

The test results for Example 3 are presented in Table 3.

Table 3:

Flow rates of R-(D_3)-tolterodine base through excised skin preparation (Example 3) Ch.-B. INZ 013)

	Content of (R,S)-tolterodine base [% by weight]	Mean cumulative flux [µg/cm^2] after		
		24 hours	48 hours	72 hours
Mouse skin (n = 4)	15.0	872.0	1388.4	1737.4
Human skin (n = 3)	15.0	165.9	490.8	784.2

Claims

1. A transdermal therapeutic system (TTS) for the transcutaneous administration of tolterodine over several days, characterised in that the TTS comprises a self-adhesive matrix material in the form of a layer, which contains a (meth)acrylate copolymer comprising ammonium groups, at least one plasticiser, and up to 25 % by weight tolterodine.

2. A transdermal therapeutic system (TTS) for the transcutaneous administration of tolterodine over several days comprising a means of fixing the TTS to the skin, characterised in that the TTS comprises a self-adhesive matrix material in the form of a layer containing tolterodine, which contains a (meth)acrylate copolymer comprising ammonium groups, at least one plasticiser and up to 25 % by weight tolterodine, and that said matrix material, with the exception of its release surface, is surrounded by a larger patch, which is free from active ingredient, for fixing to the skin at the point of application.

3. A TTS according to claims 1-2, characterised in that the matrix material which contains an active ingredient contains (R,S)-tolterodine or R-tolterodine.

4. A TTS according to claims 1-3, characterised in that the matrix material which contains an active ingredient contains deuterated tolterodine.

5. A TTS according to claims 1-4, characterised in that the matrix material which contains an active ingredient is a solid solution.

6. A TTS according to claims 1-5, characterised in that the matrix material which contains an active ingredient contains at least one triester of citric acid as a plasticiser.

7. A TTS according to claim 6, characterised in that it contains tributyl citrate, on its own or in admixture with triethyl citrate, as a plasticiser.

8. A TTS according to claims 1-7, characterised in that the backing film comprises a metallised or oxide coating on its matrix side.

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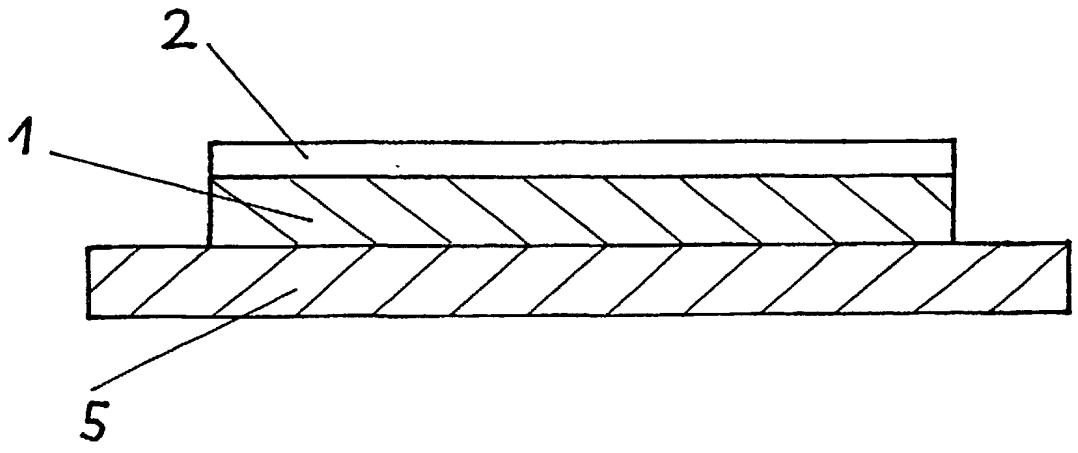
Veröffentlicht
Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.

(54) **Title:** TRANSDERMAL THERAPEUTIC SYSTEM (TTS) CONTAINING TOLTERODINE

(54) **Bezeichnung:** TRANSDERMALES THERAPEUTISCHES SYSTEM (TTS) TOLTERODIN ENTHALTEND



(57) **Abstract**

The invention relates to a transdermal therapeutic system (TTS) for transcutaneously administering tolterodine over a period of several days and to a method for producing the same. The TTS contains a self–adhesive layer–shaped matrix material which contains a (meth)acrylate copolymer comprising ammonium groups. The TTS also contains at least one softener and up to 25 wt. % of tolterodine.

(57) **Zusammenfassung**

Die Erfindung betrifft ein Transdermales Therapeutisches System (TTS) zur transcutanen Verabreichung von Tolterodin über mehrere Tage sowie ein Verfahren zu dessen Herstellung. Das TTS enthält eine selbstklebende schichtförmige Matrixmasse, die ein ammoniumgruppenhaltiges (Meth) acrylatcopolymer, mindestens einen Weichmacher und bis zu 25 Gew.–% Tolterodin enthält.

Declaration and Power of Attorney for Patent Application
English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

A TRANSDERMAL THERAPEUTIC SYSTEM (TTS) CONTAINING TOLTERODINE

the specification of which

(check one)

[X] corresponds to and claims priority of German Patent Application Serial No. 199 22 662 8 filed May 18, 1999 and PCT/EP00/04360, filed May 16, 2000.

[ ] was filed on _____ as United States Application No. or PCT Application No. _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
DE 199 22 662.8 (Number)	Germany (Country)	18 May 1999 (Day/Month/Year Filed)	[ ]
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	[ ]
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	[ ]

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below.

(Application Serial No.)	(Filing Date)

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(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
PCT/EP00/04360	16 May 2000	Pending

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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